CRYSTAL ENGINEERING

1. Introduction

Crystal engineering (CE hereafter) is the bottom-up construction of functional materials from the assembly of molecular or ionic components (1). CE applies the concepts of supramolecular chemistry (2) to the solid state. In the supramolecular approach to crystalline solids, the crystals are seen as networks of interactions. These interactions can be covalent bonds between atoms (eg, diamond, silica, and graphite) as well as coordination bonds between ligands and metal centers, Coulombic attractions and repulsions between ions, and noncovalent bonds between neutral molecules (van der Waals, hydrogen bonds, etc) or—of course—any combination of these linkages. The difference in bonding types offers a practical way to subdivide CE target materials as a function of the energy involved in *local* bond breaking–bond forming processes. These bonding

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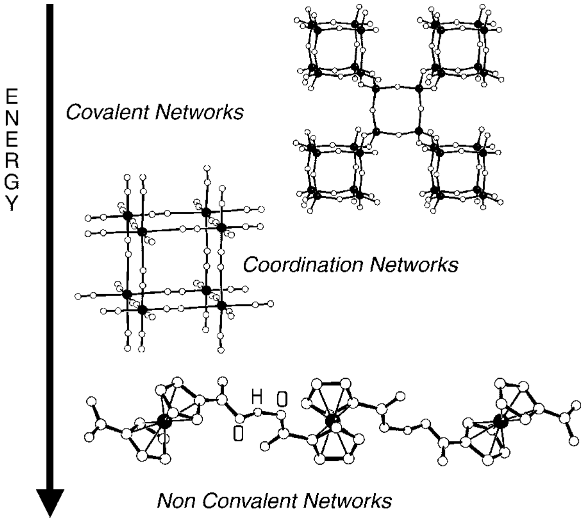

Fig. 1. An approximate ranking in the energy of covalent, coordination and hydrogen-bonded networks.

interactions follow an approximate ranking in energy: from the high enthalpies involved in breaking and forming of covalent bonds between atoms to the tiny energies involved in the van der Waals interactions between neutral atoms in neutral molecules (3) (see Fig. 1).

Even though the epithet “crystal engineering” was first used to describe solid-state photochemically activated organic reactions (see below), the directions of fastest expansions of CE are in the fields of inorganic (4), organometallic (5), and coordination chemistry (6) as it will be apparent from the proceedings.

1.1. Crystal Engineering—Historical Background. The qualifier *engineering* associated to crystals was first employed by G. Schmidt and collaborators at the Weitzmann Institute in the early 1970s to describe the photodimerization reaction of cinnamic acid and derivatives in the solid state (7). The idea was relatively simple: topochemical control on photochemical activated cyclization reactions could occur, because the double bonds of the olefins were locked in place by the crystal packing at an appropriate distance for reaction (see Fig. 2). Schmidt wrote: “*The systematic development of our subject will be difficult if not impossible until we understand the intermolecular forces responsible for the stability of the crystalline lattice of organic compounds: a theory of the organic solid state is a requirement for the eventual control of molecular packing arrangement. Once such a theory exists we shall, in the present context of synthetic and mechanistic photochemistry, be able to ‘engineer’ crystal structures having intermolecular contact geometries appropriate for chemical reaction, much as, in other context, we shall construct organic conductors, catalysts, etc.*”

In spite of many scientific efforts, however, the lack of true predictability of the arrangements that molecules with different shapes could adopt in the solid state, together with the difficulty of the solid-state characterization of the resulting products, did not yield the desired results. The epithets were rediscovered

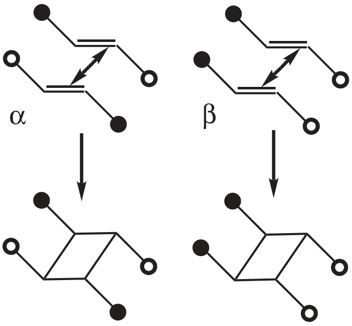

Fig. 2. A schematic representation of Schmidt's photodimerization reaction of cinnamic acid in the solid state. The proximity and adequate orientation of the reacting groups is required for the cyclization to take place.

almost two decades later. This *rebirth* is due to several reasons. First, the success of supramolecular chemistry provided the appropriate cultural environment, shifting the interest of many scientific groups from a molecular based chemistry to the chemistry of molecular aggregates. This shift was accompanied by the urge for more utilitarian objectives for the chemical sciences, such as those provided by materials chemistry as a consequence of diffuse funding restrictions for fundamental studies. Last, but not least, one has to consider the past decade progress in computing and diffraction tools that allow us to tackle on a reasonable time scale theoretical and experimental problems of great complexity, such as those associated with complex molecular solids, interdigitated networks, and supramolecular aggregates.

In 1988, Maddox wrote in a *Nature* editorial that "*One of the continuing scandals in the physical sciences is that it remains in general impossible to predict the structure of even the simplest crystalline solid from a knowledge of their chemical compositions*" (8). This statement, taken from an article concerned with *ab initio* calculations of silica, has been quoted many times to stress how far we all were from being able to understand and model the forces responsible for the cohesion of solids. At about the same time M. Etter was pointing out that "*Organizing molecules into predictable arrays is the first step in a systematic approach to designing solid-state materials*" (9). A couple of years later, G. R. Desiraju published the very first book devoted to organic crystal engineering; the term was given the following interpretation: "*The understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desired physical and chemical properties*" (10).

These hints, together with the results obtained, quite independently, by several research groups in the coordination, organic, and organometallic solid-state sciences (11–14), indicated the direction of future development: the construction of "crystalline materials with a purpose". Crystals were no longer perceived as "molecular containers", useful for the detailed determination of *molecular* structures, but as supramolecular entities with collective chemical and physical properties.

Of course crystals were prepared “with a purpose” long before the advent of *modern* crystal engineering. The properties of molecular materials have been explored extensively in studies of charge transfer (15), conductivity and superconductivity (16), magnetism (17), and nonlinear optics (18). It is, however, the supramolecular awareness that has given impetus to the field by generating useful interdisciplinary connections.

Modern crystal engineering draws its strength from the synergistic interaction between design and synthesis of supermolecules on the one hand, and design and synthesis of crystalline materials with desired solid-state properties, on the other hand. In a way, the definition of supramolecular chemistry put forward by J.-M. Lehn (19) in his Nobel lecture (*chemistry beyond the molecule bearing on the organized entities of higher complexity that result from the association of two or more chemical species held together by intermolecular forces*) seems to encompass crystal engineering. What is a (molecular) crystal if not an “organized entity of higher complexity held together by intermolecular forces”? Rather than thinking of a crystal as a “molecular container”, ie, a box, in which molecules and ions with identical characteristics and properties can be conveniently packed, synthetic chemists have begun to think in “supramolecular” terms. The *collective properties* of the aggregate depend on the choice of intermolecular and interionic interactions between components and on the convolution of the properties of the building blocks with the periodicity of the crystal.

1.2. The Ranking in Energy and the Synthetic Strategies. A topological distinction needs to be made between molecular crystal engineering, where the building blocks are clearly recognizable molecular or ionic species, and coordination and covalent crystal engineering, which often utilize building blocks that do not exist as separate entities. Coordination crystal engineering, in particular, can be seen as periodic coordination chemistry, as the ligand–metal bonding capacity is projected in two (2D) or three dimensions (3D) to form extended networks (coordination polymers) by using polydentate ligands (see Fig. 3).

A second broad difference arises from the energies involved in the construction of the different types of crystalline materials. Even though there is a continuum of intermediate energetic situations between those depicted in Figure 1, the construction of covalent networks (eg, synthetic zeolites, or intercalates) usually requires larger energies than those required to prepare coordination networks or to assemble molecular crystals. Clearly, control, reproducibility, and transferability of the small energies involved in the building up sequences of molecular crystals by means of noncovalent interactions constitute extremely challenging study subjects. Next, we will use the term *intermolecular* as a synonym of *noncovalent*, with this encompassing all types of secondary interionic or intermolecular interactions that do not imply two-electron σ bonds (eg, Coulombic interactions, hydrogen bonds, van der Waals interactions, and their combination). *Making crystals* on purpose requires an appreciation of the different energetic factors involving molecular crystals, which are held together by van der Waals interactions of the order of very few kilojoules per mole (kJ/mol), and those involving covalent bonds, which require hundreds of kilojoules per mole of energy to be broken and formed.

1.3. Crystal Engineering and Polymorphism. Before discussing CE strategies it is appropriate to mention that in many cases the crystallization

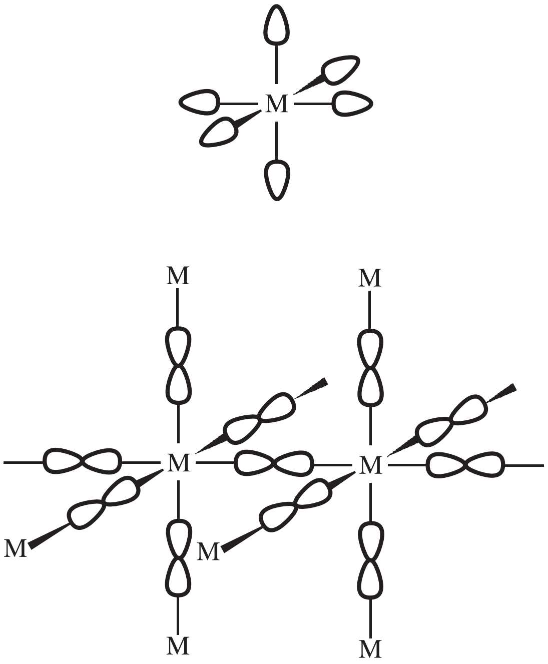

Fig. 3. From coordination complexes (**a**) to coordination networks (**b**): the use of bidentate ligand spacers allows construction of *periodical* coordination complexes.

process, such a key step of the crystal engineering endeavor, may not yield a univocal answer. Crystal polymorphism (20), ie, the existence of more than one packing arrangement for the same molecular or ionic substance(s), could be a major drawback for the purposed bottom-up construction of functional solids. However, although the discovery of polymorphs of molecular crystals or of their diverse solvate forms (*pseudo*-polymorphs) is often serendipitous, crystal polymorphism can, to some extent, be controlled. Polymorphic and pseudo-polymorphic modifications of the same substance can also be obtained by thermal and mechanical treatment and by solvation and desolvation (see below). An important discrimination is between polymorphs that interconvert via a solid–solid phase transition (enantiotropic systems) and those that melt before interconversion takes place (monotropic systems).

Conformational polymorphism occurs when a molecule possesses internal degrees of freedom, which allow the existence of different low-energy conformations, as in organic species, or different relative disposition of ligands, in a metal–organic species (21). Conformational polymorphism is a common characteristic of coordination and organometallic species, because of the often delocalized nature of the ligand–metal interactions and the consequent high conformational freedom (22). *Concomitant polymorphs* are those obtained from the same crystallization process (23). Pseudo-polymorphism refers to cases in which a given substance is known to crystallize with different amounts or types of solvent molecules (24). Even though polymorphic modifications contain exactly the same substance, they usually differ in chemical and physical properties such as density, diffraction pattern, solid-state spectroscopy, melting point, stability, reactivity, and mechanical properties.

Polymorphic modifications of a molecular crystal can be seen as *crystal isomers* arising from different distributions of intermolecular interactions. Hence, the change in crystal structure associated with an interconversion of polymorphs, ie, a solid–solid phase transition (between ordered phases), in which intermolecular interactions are rearranged, can be regarded as the crystalline equivalent of a summarization at the molecular level.

A detailed discussion of these aspects, albeit relevant, is beyond the scopes of this article. Polymorphism and pseudo-polymorphism are mentioned here only to draw the readers attention to the fact that crystallization cannot be considered, in many cases, to be a fully reproducible step of the CE strategy. A schematic representation of the relationship between polymorphic and pseudo-polymorphic forms of a molecular crystal is shown in Fig. 4.

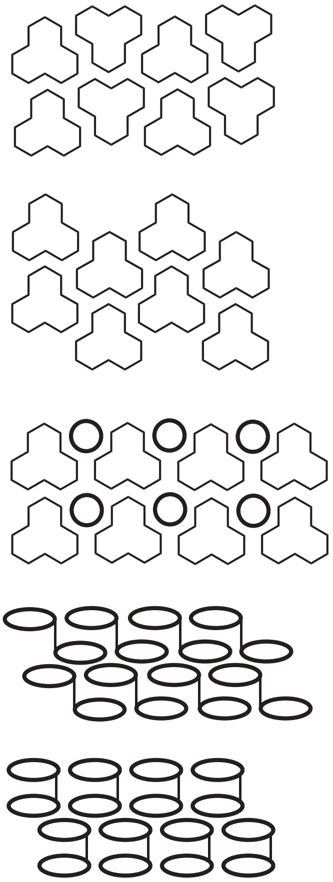

Fig. 4. Schematic representation of the relationship between polymorphic and pseudo-polymorphic forms of a molecular crystal. From top: two polymorphic modifications of the same molecular systems differing in the relative orientation of the components; a pseudo-polymorphic modification of the two ideal crystals above, the circles representing cocrystallized solvent molecules or other guests; conformational polymorphs modifications arising from conformational degrees of freedom at the molecular level.

2. An Overview of Crystal Engineering Strategies

For the sake of this discussion, we have decided to describe different CE strategies on the basis of the energetics of the interactions involved, namely, very weak noncovalent interactions (van der Waals interactions), hydrogen bonds between neutral molecules and ions, coordination bonds, etc. It should be clear, however, that all intermediate situations are possible. Irrespective of the nature of the *principal* interaction, it should be kept in mind that every crystal represents a compromise between several, often nonconverging factors, such as the optimization of intramolecular interactions versus intermolecular interactions, together with that of less directional interactions, such as those of van der Waals nature, the electrostatic terms arising from dipoles, etc, or other interactions. Moreover, formation and rupture of weak or very weak interactions between component subunits in noncovalent syntheses imply small ΔH values. Cooperativity is thus required to overcome unfavorable entropy terms in order for the supramolecular aggregation process to become thermodynamically spontaneous.

2.1. Crystal Engineering Based on van der Waals Interactions. In solids made of discrete molecules without strong dipolar moments (often oversimplified as "van der Waals solids"), the attractive forces acting between *molecules*, regarded as ensembles of atoms, fall off very rapidly with the distance. Repulsions are effective at very short distances and much dependent on the nature of the peripheral atoms, which determine the electrostatic potential hypersurface surrounding the molecule. In this way, the bulk of the molecule provides attraction, while surface atoms determine recognition, optimum relative orientation, and interlocking of molecules in the solid state. In general, a given supramolecular arrangement in the solid state can be seen as the result of the minimization of short-range repulsions, rather than the optimization of attractions. It is therefore important, when considering a molecular crystal, to focus on the relationship between molecular shape and nature of the peripheral atoms.

In the absence of directing interactions, resulting, eg, from the presence of strong dipoles or hydrogen bonding donor–acceptor groups (see below), the recognition process will be controlled by the outer shape of the molecule and by the nature of the peripheral atoms. The formation of a stable dimolecular aggregate—as the initial step of a crystallization process—whether formed by the same molecule, ie, AA, or by two different molecules/ions, ie, AB, or $A^{+/-}B^{-/+}$, will depend primarily on the complementarity of shape. This concept was put forward by L. Pauling long ago (25): "*... in order to achieve the maximum stability, the two molecules must have complementary surfaces, like die and coin, and also a complementary distribution of active groups. The case might occur in which the two complementary structures happened to be identical; however, in this case also the stability of the complex of two molecules would be due to their complementariness rather than their identity*". The interaction between van der Waals molecules with different shapes is depicted schematically in Figure 5.

An example of CE based only on van der Waals interactions is the preparation of one-dimensional (1D) van der Waals networks via calix[4]arene derivatives, bearing two receptor cavities arranged in a divergent fashion, and neutral molecules employed as linear connectors (26). The resulting 1D network,

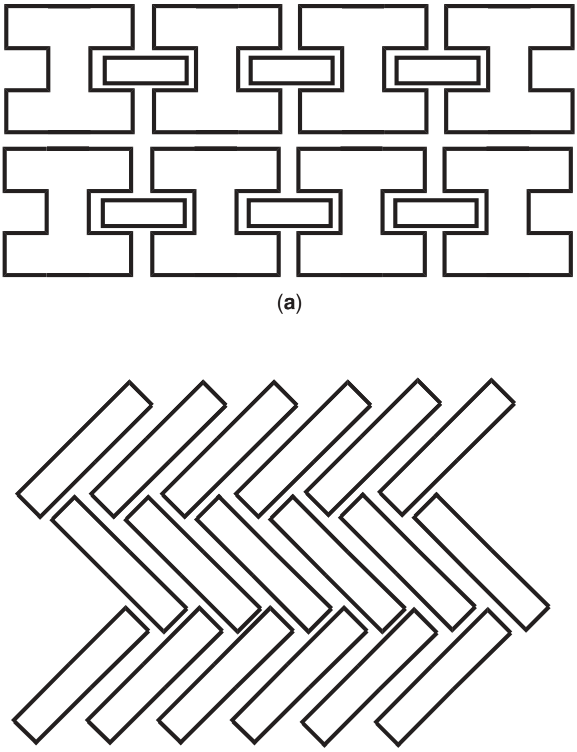

Fig. 5. (**a**) The interaction between van der Waals molecules with complementary shapes; molecules of type A can be *joined* by molecules of type B forming a van der Waals network structure; (**b**) discoidal molecules (in projection) form a herringbone pattern.

or *koilate*, is obtained by translation of the assembling core defined by the inclusion connector into the cavity of the receptor. Recognition, self-assembly, and cohesion of the solid-state networks are all based on van der Waals interactions.

van der Waals solids have been investigated theoretically (27) thanks to the availability of empirical potentials. Tests on known crystal structures of hydrocarbons have shown that, in some favorable cases, crystal structures of organic hydrocarbons can be predicted from molecular structure. The generation of theoretical crystal structures still represents a significant scientific challenge (27). However, a discussion of this aspect of crystal engineering is beyond the scope of this article.

2.2. Crystal Engineering Based on Hydrogen Bonds. The hydrogen bond is the interaction of choice in molecular crystal engineering because it combines strength and directionality (28). Strength is synonym of cohesion and stability (29), while directionality implies topological control and selectivity, which guarantee reproducibility to the supramolecular assembly process. A directional, ie, selective, intermolecular interaction possesses specific topological properties and its performance within different structural environments can be predictable.

The concept of hydrogen bond "strength" deserves a more subtle comment because it brings about the very definition of the hydrogen bond. For most purposes, the hydrogen bond can be described as a stable interaction of essentially electrostatic nature between an X–H donor and a Y acceptor, being X and Y electronegative atoms or electron rich groups (30). The hydrogen-bonding interaction is generally stronger than the strongest van der Waals interaction. $H\cdots Y$ and $X\cdots Y$ separations shorter than van der Waals contact distances and $X{-}H\cdots Y$ angles that tend to linearity are considered diagnostic of the presence of strong hydrogen bonds (31). The same topological rules are followed by hydrogen-bonding interactions between ions, even though the energetic scale is different (32). In the case of hydrogen bonding-interactions between neutral molecules the length/strength analogy is believed to hold, ie, the shorter the acceptor–donor distance the stronger the bond. This relationship, however, fails to apply satisfactorily in the case of weak and very weak hydrogen-bonding interactions (33), where the electrostatic component is active at a distance larger than van der Waals contacts, and in the case of hydrogen bonding interactions between ions, where the dominant energetic terms come from Coulombic attractions and repulsions (34). This latter aspect, in particular, is often overlooked. For the purpose of crystal engineering, however, Etter's elaboration (35) of L. Pauling definition of a bond (36) is probably the most appropriate: "*A hydrogen bond is an interaction that directs the association of a covalently bound hydrogen atom with one or more other atoms, groups of atoms, or molecules into an aggregate structure that is sufficiently stable to make it convenient for the chemist to consider it as an independent chemical species*". The focus is on the concept of "directed" association and of stability, and the existence of an intermolecular bond is conceptually associated with the energetic stability of the aggregate. In terms of energy, hydrogen-bonding interactions span a large interval, ranging from tiny energies (~10 kJ/mol in the case of $C{-}H\cdots O$, see below) to large values when the acceptor is an anion (~120–130 kJ/mol in the case of $O{-}H\cdots O^{(-)}$). Negatively charge-assisted (37a), positively charge-assisted (37b), as well as resonance-assisted (37c) hydrogen bonds have been identified. In CE, it is important to keep in mind that there is a *continuum* of energy, hence the distinction between strong and weak hydrogen bonds often is only conventional, and there is a difference between hydrogen-bonding interactions involving ions and those involving neutral molecules in crystals because of the differences in physical properties (solubility, melting point, behavior under mechanical stress, etc) arising from the presence of ions or neutral molecules.

In general, strong donor–acceptor groups such as –COOH and –OH systems, as well as primary $-CONH_2$ and secondary –CONHR amido groups, form essentially the same type of hydrogen-bonding interactions (Fig. 6) whether as part of organic molecules or of metal coordinated ligands. This is not surprising, as hydrogen bonds formed by such strong donor and acceptor groups are at least one order of magnitude stronger than most noncovalent interactions and are most often already present in solution.

For the purposes of CE, the utilization of a single very strong interaction, such as the $O{-}H\cdots O^{(-)}$ mentioned above, is not necessarily the best or only way to provide cohesion. The "*Gulliver effect*" can also be exploited: The collective strength of weaker bonds may be equivalent, in terms of cohesion, to the strength

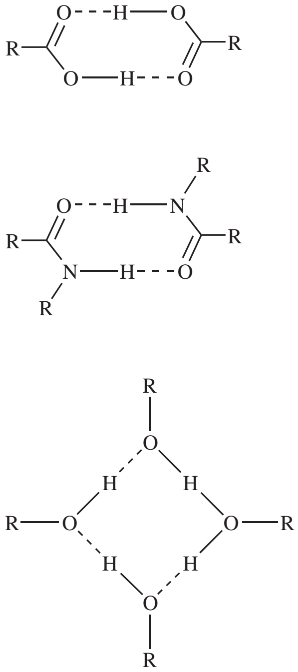

Fig. 6. Strong donor–acceptor groups such as R–COOH, R–CONHR, and R–OH form the same type of hydrogen-bonding interactions whether as part of organic molecules or of metal coordinated ligands, R = organic, inorganic, organometallic, or coordination compound.

of a single bond, although the directionality component may be lost or greatly diminished. A selection of hydrogen-bonding interactions involving strong and weak donor/acceptor groups in organic molecules and coordination complexes is reported in Figure 7.

Hydrogen bond oriented CE represents a vast portion of the literature on molecule-based crystal construction. Undoubtedly, a prototypical hydrogen-bond motif is the carboxylic ring and those topologically related, such as the amide ring and the diboronic acid ring (see Fig. 8). The reason for this preference is due to the high reproducibility and transferability of these motifs from crystal to crystal, which is maintained also when the functional group is part of a larger molecular system or metal bound ligand.

2.3. Hydrogen Bonding and Crystal Engineering Involving Neutral Molecules. The *usefulness* of hydrogen-bonding interactions in CE is a direct function of the strength and predictability of the interaction; for this reason CE applications based on weak hydrogen bonds (38) are less frequent. Weak hydrogen bonds, such as C–H···O, C–H···N, or C–H···π are more important as ancillary interactions, whose optimization often determines the fine tuning of the crystal packing, while molecular recognition and self-assembly are controlled by the stronger and more directional interactions. Nonetheless, optimization of weaker interactions may have dramatic consequences on the molecular

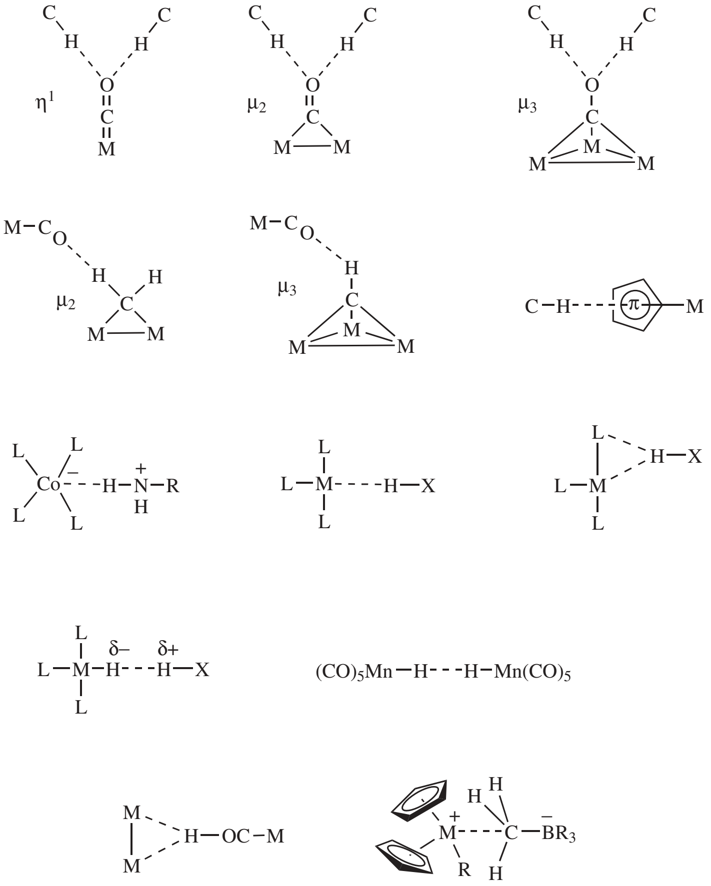

Fig. 7. Hydrogen-bonding interactions involving metal coordinated ligands. From left to right: terminal, edge-bridging, face-bridging hydrogen-bonding acceptor CO ligands; methylene μ_2-CH_2, methylidyne (μ_3-CH) hydrogen-bonding donor ligands; $-CH\cdots\pi$ interaction involving a metal coordinated cyclopentadienyl ligand; charge-assisted $[Co(CO)_4{}^-]\cdots[H{-}NR_3]^+$ hydrogen-bonding interaction involving an electron-rich Co acceptor atom; intermolecular hydrogen-bonding interactions involving electron-rich metal atoms and main group elements, electrostatic and covalent dihydrogen-bonding interactions, metal bound hydrogen atom acting as hydrogen-bonding donor toward a metal bound CO−ligand acceptor, intermolecular *pseudo*-agostic interactions involving an unsaturated electron deficient metal center.

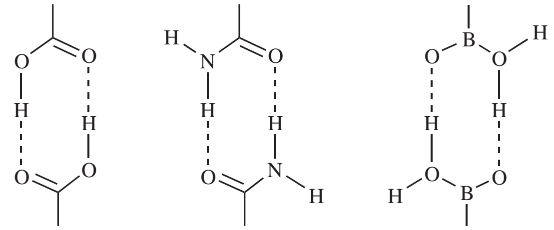

Fig. 8. The topological relationship between the hydrogen-bonded carboxylic, amide, and diboronic acid rings.

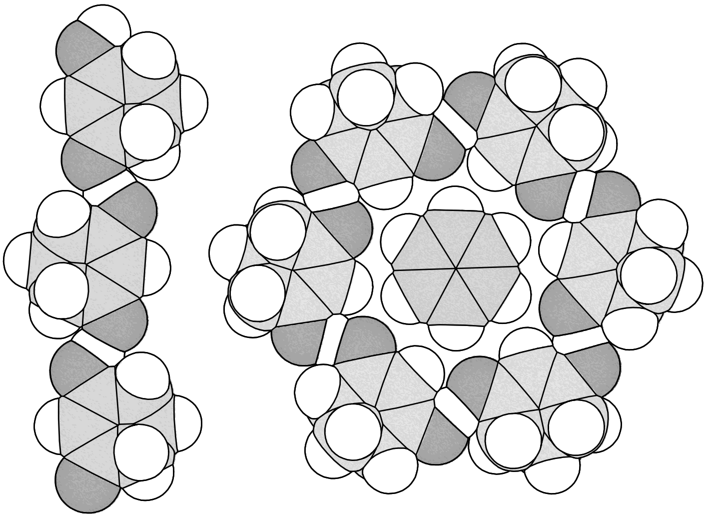

Fig. 9. Crystallization of 1,3-cyclohexanedione ($C_6H_8O_2$) from THF leads to formation of O−H···O hydrogen-bonded chains (**a**), while crystallization from benzene forms hexameric units encapsulating benzene (**b**) (39b).

arrangement in the solid state. An example is provided by the work of Etter and co-workers (39a) with the molecule 1,3-cyclohexanedione ($C_6H_8O_2$). 1,3-Cyclohexanedione forms O−H···O hydrogen bonded chains if crystallized from tetrahydrofuran (THF) (Fig. 9**a**), but it forms hexameric units (Fig. 9**b**) when the crystallization solvent is benzene. Even though the dominating interactions are still the O−H···O hydrogen bonds between dione molecules, the interactions with benzene, which acts as a templating unit, occur via C−H···O interactions. The interaction between the benzene molecule and the cyclamer can be mimicked by replacing benzene with bis-[benzene chromium(I)] (39b). The organic and organometallic molecules possess a similar discoidal shape. The difference between the benzene cyclamer and the bis-[benzene chromium(I)] adduct $[Cr^I(\eta^6-C_6H_6)_2]^+[(C_6H_7O_2)(C_6H_8O_2)]\cdot(C_6H_8O_2)_2$ resides mainly in the nature of the interaction, which is essentially Coulombic in the latter compound.

The supramolecular principle of directed self-assembly of molecules containing complementary hydrogen-bonding groups has been widely exploited. As an example of hydrogen-bonding interactions between neutral coordination complexes, it is worth citing the work by Brammer and co-workers (40), where metal coordinated arene ligands are employed, bearing hydrogen-bonding functional groups that exploit the directionality of these interactions to direct the self-assembly and construction. The hydrogen-bonding groups present as substituents on the arene ring direct the assembly and propagation in the crystal structure. This approach has been used with compounds of the series $[Cr\{\eta^6-C_6H_{6-n}(CO_2H)_{(n)}\}(CO)_3]$, with $n = 1–3$ (see Fig. 10). Several other examples can be found in the papers quoted above or in review articles (41).

2.4. Crystal Engineering with Hydrogen Bonds Between Ions. A practical instrument in devising new solids is provided by the combined use of

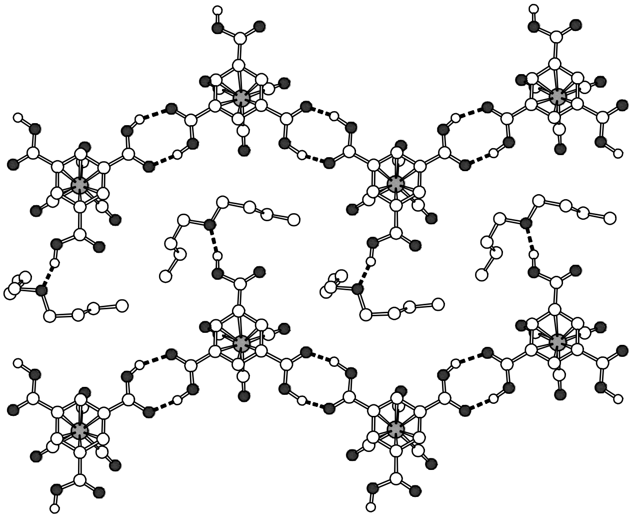

Fig. 10. The hydrogen-bonded array formed by the neutral complex [Cr{η^6-$C_6H_3(CO_2H)_3$}$(CO)_3$] · n-Bu_2O (40).

ionic charges (viz, Coulombic interactions) and hydrogen-bonding interactions. Since the hydrogen bond has a fundamentally electrostatic nature, the presence of ionic charges on the building blocks can be exploited to strengthen the interaction. *Charge assistance* to hydrogen bond is the enhancement of donor and acceptor systems polarity by utilizing cationic donors and anionic acceptors instead of neutral systems, ie, $X{-}H^{(+)}\cdots Y^{(-)}$ rather than $X{-}H\cdots Y$. The favorable location of ionic charges enhances both proton acidity *and* acceptor basicity in the solid state. Hydrogen-bonding interactions between ions optimally convolute the strength of the Coulombic field generated by the ions with the high level of directionality afforded by the $X{-}H\cdots Y$ interaction. The relationship is shown in Figure 11.

There are essentially two distinct strategies that utilize acid–base reactions to construct crystals via charge-assisted hydrogen bonds between ions:

1. Formation of *hetero*-ionic interactions. Protonation of nitrogen containing bases (amines, aminidines, etc), upon reaction with polycarboxylic acid molecules, eg, $RCOOH + NR_3 \rightarrow RCOO^{(-)}\cdots{}^{(+)}HNR_3$, lead to formation of strong $N{-}H^{(+)}\cdots O^{(-)}$ interactions, hence to anion–cation pairing in the solid state. Depending on the acid–base stoichiometric ratio, $N{-}H^{(+)}\cdots O^{(-)}$ and $O{-}H\cdots O^{(-)}$ hydrogen-bonding interactions may be present simultaneously.
2. Formation of *homo*-ionic interactions. The base cannot form hydrogen-bonding interactions with the acid moiety. This is the case of the reaction of polycarboxylic acids with bases that do not carry strong acceptor–donor hydrogen-bond groups. The $-COOH$ groups, which remain on the polycarboxylic acids after partial deprotonation, lead to self-assembly of the acid anions via $O{-}H\cdots O^{(-)}$ and ${}^{(-)}O{-}H\cdots O^{(-)}$ interactions. By choosing the

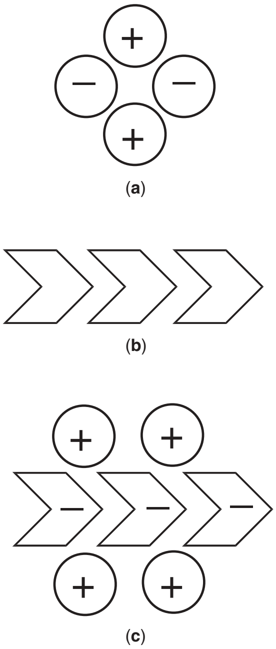

Fig. 11. The relationship between directionality and strength in charge-assisted hydrogen-bonding interactions. (**a**) The interaction between ions is strong but poorly directional. (**b**) The interaction between neutral molecules forming hydrogen bonds (represented by the arrows) is highly directional but weak. (**c**) The hydrogen-bonding interaction between ions in the presence of cations combine the strength of the Coulombic field with the directionality of the hydrogen-bonding interaction.

number of carboxylic groups (hence, the number of potential donor−acceptor systems) and the stoichiometric ratios in the acid−base reactions, one can control the formation of $O-H\cdots O^{(-)}$ and/or $^{(-)}O-H\cdots O^{(-)}$ interactions, hence homoionic self-assembly. The two situations are shown in Figure 12.

Ward's "soft" molecular host networks combine two relatively simple structural units: Layers of guanidinium cations spaced by pillars of sulfonate anions (see Fig. 13) (42). The $^{(+)}N-H\cdots O^{(-)}$ interactions between guanidinium cations and sulfonate anions render the superstructures at the same time robust and adaptable to the guest requirements, while the porosity can be tuned by changing the length of the pillars. These properties have been exploited in several applications, such as shape-selective separation of molecular isomers.

Orpen and co-workers (43) developed the use of salts of perhalometallate complexes $[MX_n]^{m}-$ ($X = Cl$, Br, etc; $M = Pt$, Zn, Mn, Pb, etc) with organic cations possessing N−H hydrogen-bond donor functionality. These systems are modular and robust and offer the opportunity to exploit the shape, charge, and functional groups of the ions in order to control the crystal structures they form and in particular the hydrogen-bond networks they contain. Chiral crystals based on hydrogen L-malate anions have been assembled via $^{(-)}O-H\cdots O^{(-)}$ bridges in anionic layers (44). Since the 2D network is highly reproducible, it can be transferred

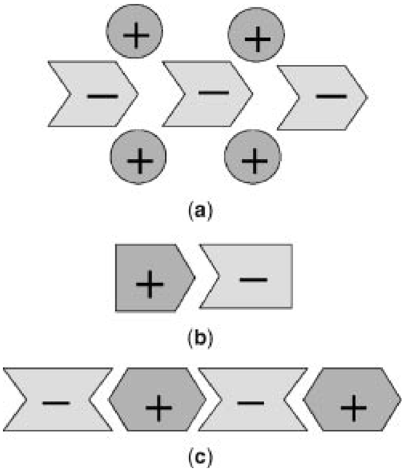

Fig. 12. Possible results of the acid–base reaction: (**a**) Self-aggregation via hydrogen-bonding interactions (represented by arrows) of the anionic units, eg, the formation of the monoanionic chain $[HC_2O_4^{(-)}\cdots HC_2O_4^{(-)}\cdots]_n$ resulting from the reaction between KOH and $H_2C_2O_4$; (**b**) ion-pairing via "charge-assisted" hydrogen-bonding interactions between cation and anion, eg, ion pairing of a monocarboxylate anion and an ammonium cation, from the reaction between a monocarboxylic acid and ammonia; (**c**) alternation of cations and anions linked via "charge-assisted" hydrogen-bonding interactions, eg, the infinite chain of alternating carboxylates and protonated diamines resulting from the reaction between a polycarboxylic acid and a diamine.

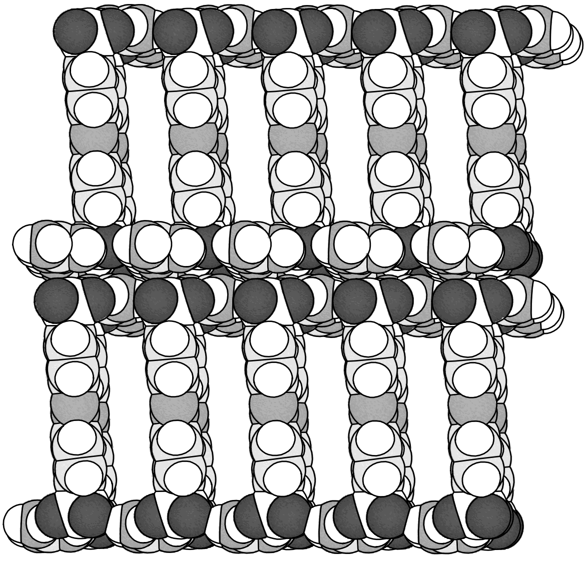

Fig. 13. An example of the utilization of charge-assisted hydrogen-bonding interactions to obtain a channeled architecture (42): In the guanidinium-sulfonate superstructure the fundamental interaction responsible for both robustness and flexibility is a charge-assisted $^{(+)}N{-}H\cdots O^{(-)}$ hydrogen bonding between the guanidinium cations and the sulfonate anions, which can be varied in shape and length.

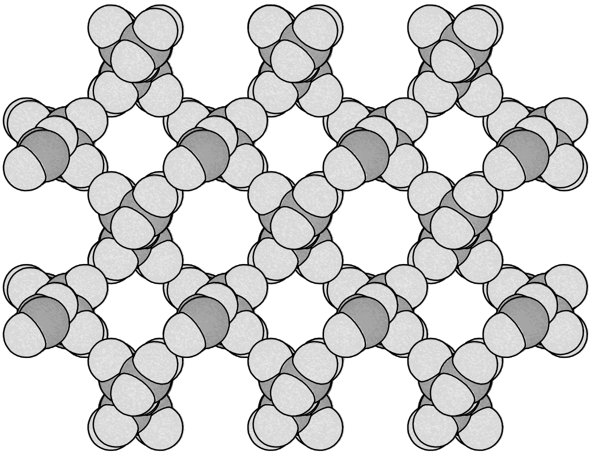

Fig. 14. The chiral honeycomb network obtained with L-tartaric acid when reacting the acid with the organometallic hydroxide $[Co^{III}(C_5H_5)_2][OH]$ (H atoms and cations occupying the channels are not shown for clarity) (45).

from crystal to crystal inducing noncentrosymmetry, a target on the route to materials for second harmonic generation.

We have used analogous strategy to self-assemble chiral frameworks around organometallic cations (45). The network obtained in the reaction of $[Co^{III}(C_5H_5)_2][OH]$ with L-tartaric acid is shown in Figure 14.

Lehn and co-workers (46) used interionic hydrogen bridges to direct the recognition and self-aggregation of metal complexes carrying terpyridine derived ligands joined by intercation $^{(+)}N{-}H\cdots N^{(+)}$ bridges. The solid-state arrangement of the $[Co(terpy)_2]^{2+}$ (terpy = 2,2′:6′,2″-terpyridine) complex is highly dependent on the choice of counterion: in the $[PF_6]^-$ salt a 2D infinite network is formed via pairs of $N{-}H\cdots N$ interactions, while in the $[BF_4]^-$ salt an interrupted network is observed. This provides an example of competition between formation of $N{-}H\cdots N$ interactions and optimization of the Coulombic interactions that, in turns, depend on the size of the ions.

In addition, hydrogen-bonding interactions between ions have been utilized to construct cages able to encapsulate alkali cations by exploiting formation of $O{-}H\cdots O$ bonds between molecules of the neutral zwitterionic complex $[Co^{III}(\eta^5\text{-}C_5H_4COO)(\eta^5\text{-}C_5H_4COOH)]$. When water solutions of $[Co^{III}(\eta^5\text{-}C_5H_4\text{-}COOH)_2]^+\cdot[PF_6]^-$ are treated with alkali metal hydroxides MOH (M = K, Rb, Cs) in 1:1 stoichiometric ratio, the acid cation is partially deprotonated and the zwitterionic form is generated. A similar acid–base reaction occurs upon treatment of aqueous $[Co^{III}(\eta^5\text{-}C_5H_4COOH)_2]^+[PF_6]^-$ with concentrated ammonia. The resulting solution contains, beside the zwitterion, the alkali or ammonium cation and the $[PF_6]^-$ anion. Upon crystallization, the zwitterion forms nearly isomorphous supramolecular aggregates with the inorganic salts $M^+[PF_6]^-$ ($M^+ = K^+$, Rb^+, Cs^+) and with $[NH_4]^+[PF_6]^-$ (47), as shown in Figure 15.

$N{-}H\cdots O$ interactions between *trans*-1,2-diaminocyclohexane and 1,2-diols have been exploited by Hanessian and co-workers (48a) to construct supramole-

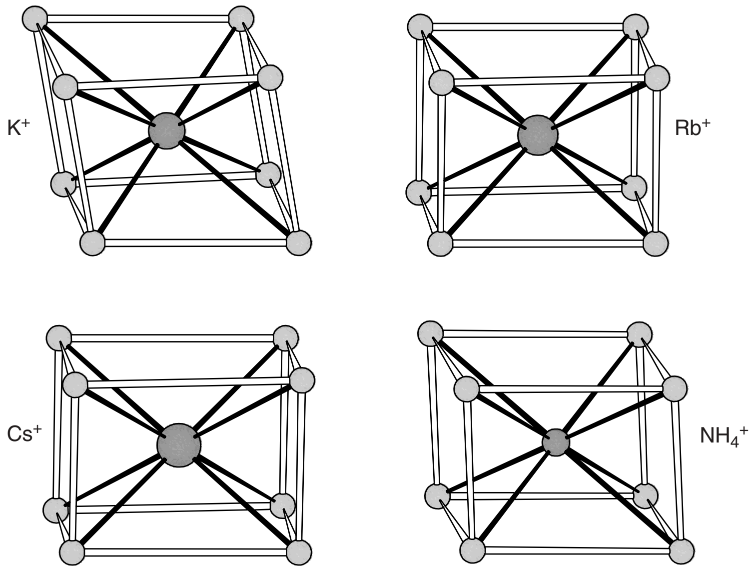

Fig. 15. The cages formed by four $[Co^{III}(\eta^5\text{-}C_5H_4COO)(\eta^5\text{-}C_5H_4COOH)]$ neutral molecules around the alkali and ammonium cation in crystalline $[Co^{III}(\eta^5\text{-}C_5H_4COO)(\eta^5\text{-}C_5H_4COOH)]\ M^+[PF_6]^-$ ($M^+ = K^+$, Rb^+, Cs^+) and $[Co^{III}(\eta^5\text{-}C_5H_4COO)(\eta^5\text{-}C_5H_4COOH)][NH_4]^+[PF_6]^-$ (47) Small spheres represent the $O_{COO/COOH}$ atoms interacting with the encapsulated cation.

cular helicate structures, which, depending on the chirality of the diols, can be left or right handed. Hydrogen-bonding interactions between ions have been exploited also by Beatty in the construction of a series of compounds containing the monoanion of 3,5-pyrazoledicarboxylic acid and ammonium-based counterions (48b). The cations contain short-chain alkyl, long-chain alkyl, phenyl, and chloro-, methoxy-, and amine-substituted aryl groups. The anions form anionic sheets to which the cations connect through hydrogen bonds.

2.5. Crystal Engineering Involving Metal Containing Species.

In recent years the utilization of metal-containing compounds in CE application has represented the turning point of the discipline, because of the wide variety of combination of spin, charge, oxidation state, topology, let alone the specific chemical reactivity afforded by coordination compounds (49,50). The role of metal atoms in CE is both electronic and structural. Distinct *functions* of metal atoms can be identified:

1. A topological function: The coordination geometry around the metal centers can be used *to preorganize in space* the *intermolecular* bonding capacity of the ligands (51).
2. An electronic function: The electronics of metal–ligand bonding interactions, such as donation and back-donation, permit tuning of ligand polarity and acid–base behavior (52).
3. A (tunable) electrostatic function: Metal atom variable oxidation states and/or the utilization of nonneutral ligands permit “charge assistance” to weak bonds.

4. Direct participation of metal atoms in intermolecular bonds: electron deficient metal atoms may accept electron density intermolecularly from suitable Lewis bases, while electron-rich metal atoms may have sterically unhindered lone pairs that accept hydrogen bonds (53).
5. A templating function: *Size and shape* of complexes may be used to template self-assembly of organic, inorganic and organometallic molecules or ions into mono-, di-, and 3D superstructures.

2.6. Crystal Engineering with Coordination Networks. Nowadays, coordination network engineering takes the "lion's share" of the scientific endeavors in the field of CE. The strategy underlying the work in this area was outlined by Robson: "*Carefully designed connecting ligands capable of binding metal centers strongly and predictably at chelation sites may afford improved structural control in network assembly*" (11,54). The basic idea is that of utilizing the coordination bonding capacity of transition-metal atoms to build supramolecular arrangements in 3D; the result is the convolution of coordination chemistry with crystal periodicity, ie, periodic coordination chemistry. The bidentate or polydentate organic ligands exert the function of spacers and linkers between metal centers; they also represent, topologically, the joints and knots holding together the networks. A schematic representation of how 1D, 2D, and 3D superstructures can be obtained by linking together metal centers via adequately chosen ligand spacers in shown in Figure 16.

The phenomena of *self-entanglement* and *interpenetration* represent the major obstacles to the preparation of crystalline materials with large and accessible empty space. The problem has been examined by several researcher groups (54,55). A schematic representation of network interpenetration is shown in Figure 17.

The most popular ligands are bidentate bipyridyl-type ligands, because of their well-known capacity for strongly binding late transition metals, leading to robust superstructures. Many strategies to construct coordination networks utilize bipyridyl-type ligands (N···N ligands, hereafter) with *at least* two N donors in suitable geometrical position to act as a bridge between metal atoms such as Ag(I), Cu(I), Ni(II). This combination ensures not only formation of robust –M–(N···N)–M–(N···N)– networks, but also the possibility of varying the network topology by choosing the proper number of donors and the geometries of the ligands. In such a way, 1D, 2D, and 3D superstructures can be obtained (56,57). The voids in the superstructures are usually filled either by self-entanglement of the networks or by inclusion of solvent or other guest molecules (58,59). Some degree of success in the exploitation of this type of artificial nanoporosity has been attained when the crystal structure nucleates and grows together with "removable" guest molecules.

However, the architecture may collapse upon removal of solvent or guest molecules. A goal of CE is, therefore, that of preparing highly porous materials that can withstand exchange of the guest molecules. Remarkable results have been obtained by Yaghi and co-workers (60): The use of bridges based on metal carboxylate clusters provides the necessary rigidity for the construction of open and robust framework structures. To this end, "paddle wheel" clusters $M(O_2CR)_4$

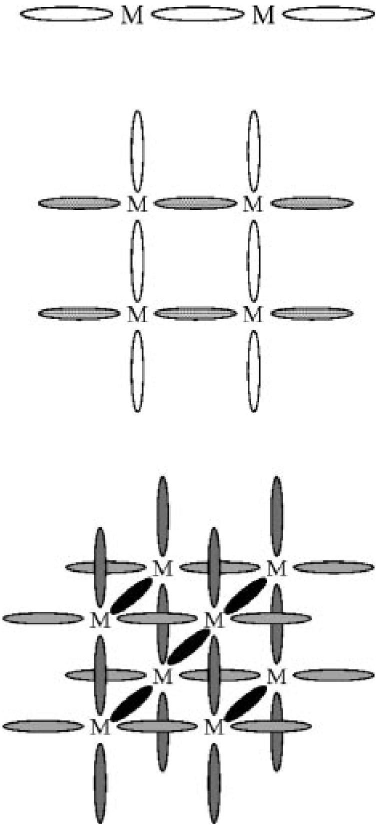

Fig. 16. A schematic representation of how 1D, 2D, and 3D superstructures can be obtained by linking together metal centers via adequately chosen ligand spacers.

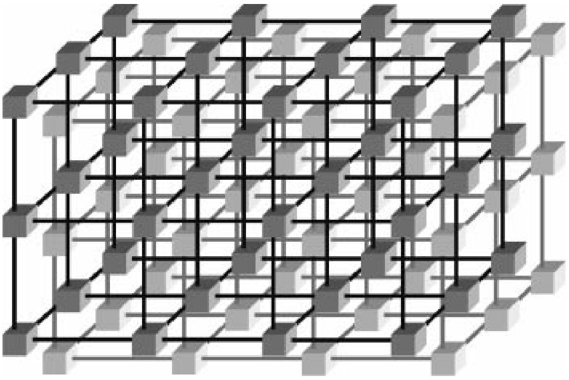

Fig. 17. Schematic representation of the interpenetration of coordination networks.

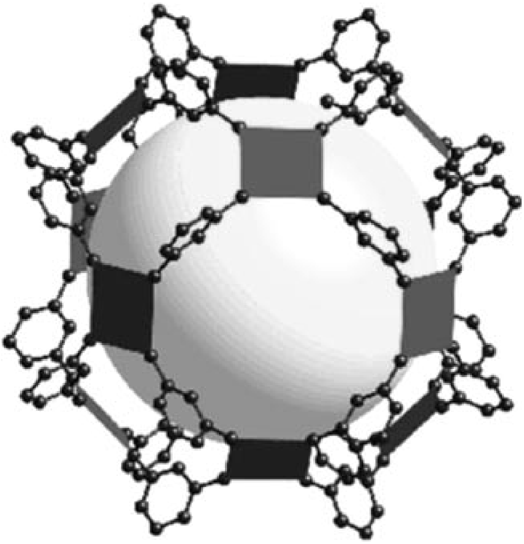

Fig. 18. “Paddle wheel” clusters $M(O_2CR)_4$ have been used to produce low density structures that can take up a large amount of guest molecules; the large sphere indicates the empty space in the crystal structure (60).

have been used to produce low density structures (see Fig. 18) whose open space represents up to 91% of the crystal volume and with cavity size that can be incrementally varied from 3.8 to 28.8 A^3. These compounds can take up a very large amount of guest molecules, and could be tested for methane storage at room temperature (60).

An important area of coordination networks is that constituted by porphyrin and metalloporphyrin systems (61). These supramolecular assemblies not only afford alternative ways for the construction of crystalline materials with large channels and cavities that mimic inorganic zeolites (61d) but are also investigated as model systems of light-harvesting and as molecular receptors and sieves (61e).

2.7. Crystal Engineering with Coordination Networks and Hydrogen Bonds. Metal–ligand coordination and hydrogen-bonding interactions, although very different in electronic nature, possess high directionality features. Since directionality is essential for a controlled assembly of the components, the topological properties of both types of interactions can be exploited simultaneously in the construction of molecular solids with predefined architectures. The simplest approach utilizes ligands that, besides being able to coordinate to the metal centers, can also establish intermolecular hydrogen-bonding interactions (62). The simultaneous utilization of coordination bonds and hydrogen bonds affords an intermediate strategy whereby coordination complexes are linked via intermolecular hydrogen bonds. Whether these interactions are between neutral molecules or between charged species will, of course, depend on the electronic nature (oxidation state) of the metal center and on the formal charge carried by the ligands. This strategy allows combining the chemical and

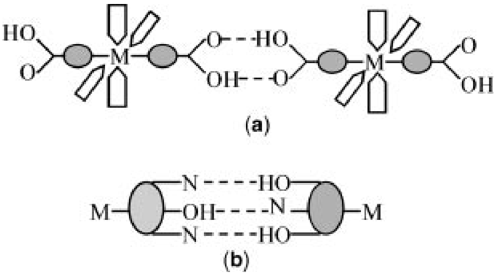

Fig. 19. A schematic representation of hydrogen-bonded networks involving coordination compounds. (**a**) A 1D structure can be obtained by using hydrogen-bonding ligands in trans-coordination. (**b**) A triple hydrogen-bond motif can be used to guarantee robustness.

physical properties of coordination compounds with the features of typical organic solids. Since many coordination complexes are ions, the counterions often play a fundamental role in determining the topology of the superstructures that can be constructed. A schematic representation of hydrogen-bonded networks of coordination compounds is shown in Figure 19, together with an example of triple hydrogen bonds.

Aakeröy and co-workers (63) used the assembly of inorganic–organic architectures through a combination of copper(I) coordination polymers and self-complementary hydrogen bonds. The design strategy yields lamellar inorganic–organic hybrid materials (see Fig. 20). Infinite copper(I) halide coordination polymers provide robust 1D building blocks, and these are subsequently linked into 2D layers via a pyridine ligand attached to each metal ion. The ligand, which also carries a self-complementary hydrogen-bond moiety (eg, carboxylic acid, carboxamide, oxime), provides a noncovalent directional tool for connecting neighboring coordination polymers into an extended 2D network.

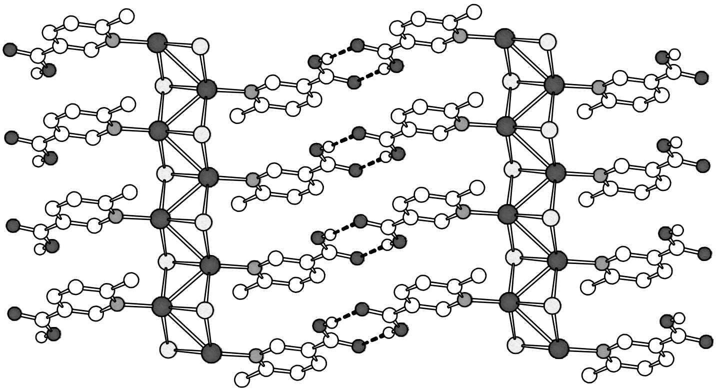

Fig. 20. A metal bound pyridine ligand carrying a carboxylic group provides a noncovalent directional tool for connecting infinite copper(I) halide coordination polymers into an extended 2D network (63).

3. Applications of Crystal Engineering

The paradigm of CE is *making crystals with a purpose*. The fulfillment of this goal depends on the interests, tastes and objectives of the investigator. The motivations can be driven by fundamental scientific curiosity or even aesthetic motivations (64), but, most often, they are utilitarian, ie, focused on making materials with useful properties. The principle of assembling building blocks to obtain functional superstructures naturally confines these properties to those of molecular materials, with this also encompassing the assembly of molecular ions. In the supramolecular approach to functional materials the properties are *collective* properties, arising from the convolution of molecular–ionic properties of the individual building blocks with the periodicity of the crystalline material. A nonexhaustive list of possible target properties is shown in the following; some key references are also reported. In the case of coordination networks (70,71), the properties that can be attained depend not only on the nature of the "nodes" and "spacers" but also on the dimensionality of the network (whether 1D, 2D, or 3D) and on the geometry of the cavities and channels.

The relationship between chemical composition and topology and some target properties or applications of engineered molecular crystals.

Target materials	References	Target properties
chiral crystalline materials and chiral frameworks	65,66	nonlinear optics, second harmonic generation
crystalline materials containing mixed-valence–spin metal atoms	67,68	molecular magnets and conductivity
crystalline materials based on π stacking interactions	69	charge transfer—conductivity
crystalline materials with channels and cavities (honeycombs, zeotypes)	54–60, 70–71	nanoporosity—molecular traps—molecular sieves

4. Solid-State Reactivity

Besides applications in molecular materials chemistry, however, CE encompasses some traditional branches of solid-state sciences. As pointed out in the Introduction, CE initiated from an investigation of solid-state reactions, and indeed the understanding of the way molecules self-recognize and self-aggregate in the solid is the first step to devise novel solid-state processes. Importantly, most reactions occurring between solids or involving solids are solvent-free (72). Because of the strive for environmentally benign reaction conditions, the use of solvent-free conditions is attracting a wide interest (73). Another goal of great interest is the exploitation of solid–gas reactions as alternative routes for the construction of molecular traps, sieves, and sensors. The investigation of the reactivity of molecular crystals lies close to the origins of crystal engineering and is at the heart of the pioneering work of Schmidt. The idea is that of organizing molecules in the solid state using the principles of molecular recognition and self-assembly. Successful results have been obtained with bimolecular reactions, particularly [2 + 2] photoreactivity and cyclization (74).

Diverse applications of host–guest chemistry in a variety of crystalline organic inclusion compounds have been described (75). For example, inclusion compounds, in which chiral crystal structures are obtained from racemic or achiral molecules, have been investigated, with application of such compounds to the synthesis of species in which the crystal structure chirality is imprinted upon the achiral molecular components (76). When achiral molecules cannot be arranged in a chiral form in the crystal, they can be arranged in a chiral form in inclusion complex crystals with a chiral host compound. Reaction of the inclusion complex in the solid state has been shown to give the optically active compound (77).

Another important application of CE is in the investigation of reactions between engineered molecular solids and molecules in the vapor phase (see Fig. 21). Heterogeneous gas–solid reactions are well known in chemistry thanks to the pioneering work of Curtin and Paul (78). It is important to appreciate that in the case of reactions between gases and solids the costs of removing and reprocessing solvents are eliminated. This goes along with the great pressure on developing solvent-free, ie, environmentally more friendly, reactions.

Uptake and release of solvent molecules (solvation, hydration) can often be paralleled to solid–gas reactions, whereby the reactants are, respectively, the molecules in the crystalline solid and in the gas phase, and the product is the solvated crystal (79). Clearly, the same reasoning applies to the reverse process, ie, generation of a new crystalline form by means of gas release. In gas–solid reactions, gases are reacted directly with crystals or amorphous phases to give solid products, often in quantitative yields (80).

A well-known case study is the reaction of crystalline benzoic acid with ammonia. The reaction leads to quantitative formation of a 1:1 ammonium

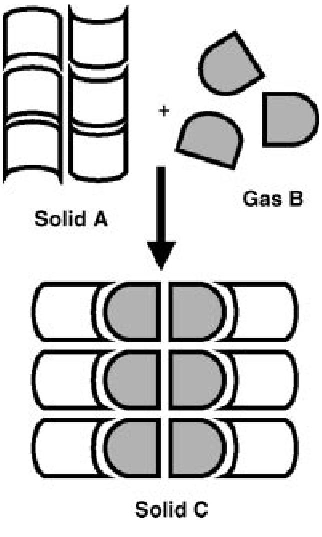

Fig. 21. Schematic representation of the formation of a new solid molecular by solid–gas reaction and/or by vapor uptake and solvate formation.

salt. Curtin and Paul were able to demonstrate that certain crystal faces are attacked preferentially by the ammonia vapor, and the resulting reaction front travels more rapidly through the crystals along directions corresponding to specific molecular arrangements (81,82). Crystalline *p*-chlorobenzoic anhydride reacts with gaseous ammonia to give the corresponding amide and ammonium salt (83); similar reactions have been investigated in the case of optically active cyclopropane carboxylic acid crystals (84).

Kaupp and co-workers (85) explored a series of solid-state reactions in which gaseous amines are reacted with aldehydes to give imines. Analogous reactions with solid anhydrides, imides, lactones or carbonates, and isothiocyanates have been used to give, respectively, diamides or amidic carboxylic salts or imides, diamides, carbamic acids, and thioureas. In a number of cases investigated, the yields were found to be quantitative. Ammonia and other gaseous amines, in particular methylamine, have also been shown to aminolyze thermoplastic polycarbonates. Such degradation processes have a high impact on the stability of data storage compact disks (86). In all these cases, it has been demonstrated that the possibility of obtaining quantitative reactions depends on the way molecules are organized in the crystal structure.

Gaseous acids have been shown to form salts with strong and weak solid nitrogen bases. Solid hydrohalides are formed quantitatively by reaction with vapors of HCl, HBr and HI; the same applies to dibases such as *o*-phenylendiamines. The products are much more easily handled than when they are formed in solution. The solid products can in turn be used to react with gaseous acetone to form the corresponding dihydrohalides of 1,5-benzodiazepines (87).

The possibility of *switching* between neutral and charged hydrogen bonding interactions is at the basis of the reversible gas-trap system obtained on reacting the cobalticinium zwitterion $[\mathrm{Co^{III}}(\eta^5\text{-}\mathrm{C_5H_4COOH})(\eta^5\text{-}\mathrm{C_5H_4COO})]$ with *both* acid and base vapors (HCl, CF_3COOH, HBF_4, and NH_3, NH_2Me, NMe_3) (88). The salts resulting from the heterogeneous reaction contain the organometallic moiety either in its fully protonated form $[\mathrm{Co^{III}}(\eta^5\text{-}\mathrm{C_5H_4COOH})_2]^+$ (in the reaction with acids) or in its fully deprotonated form $[\mathrm{Co^{III}}(\eta^5\text{-}\mathrm{C_5H_4COO})_2]^-$ (in the reaction with bases), as shown in Figure 22. The two types of reactions imply the interconversion between neutral $\mathrm{O{-}H\cdots O}$ hydrogen-bonding interactions and $^{(+)}\mathrm{O{-}H\cdots X^{(-)}}$ and $^{(-)}\mathrm{O\cdots H{-}N^{(+)}}$ interactions, respectively.

Another relevant example of the use of crystalline coordination compounds to sense and trap molecules is that provided by van Koten and co-workers (89). It has been shown that self-assembled organoplatinum(II) complexes, containing N,C,N terdentate coordinating anion “pincers”, reversibly and quantitatively bind gaseous SO_2 in the solid state by Pt−S bond formation and cleavage, giving five-coordinate adducts. The five-coordinate adduct is also crystalline and the reverse reaction, namely, the release of SO_2, does not destroy the crystalline ordering. The Pt-complex can thus be seen as a crystalline supermolecule able to switch “on” and “off” as a direct response to gas uptake and release.

It can be argued that the *reaction* of a molecular solid, whether formed of organic, organometallic molecules or coordination compounds, with a vapor is conceptually related to the *supramolecular reaction* of a crystalline material with a volatile solvent to form a new crystalline solid (Fig. 21). Indeed, the two processes, solid−gas reaction and solid−gas solvation, differ only in the energetic

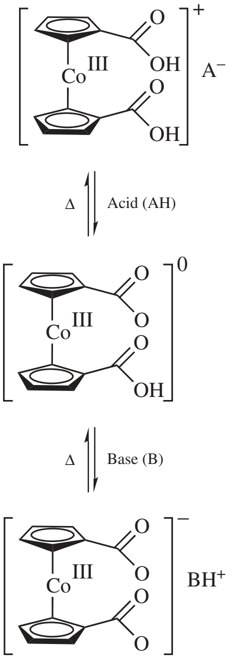

Fig. 22. Reversible gas–solid reactions of the organometallic species [Co^{III}(η^5-C_5H_4COOH)(η^5-C_5H_4COO)] with vapors of both acids (HCl, CF_3COOH, HBF_4) and bases (NH_3, NH_2Me, NMe_3) (88).

ranking of the interactions that are broken or formed through the processes. In solvation–desolvation processes, one is dealing mainly with noncovalent van der Waals or hydrogen-bonding interactions, while in chemical reactions covalent bonds are broken or formed.

This awareness is useful to devise CE studies whereby gas uptake is exploited not only to produce new crystalline forms of a given substance but also as a means to produce new materials in crystalline form. Clearly, the conceptual borderline between the two types of processes is very thin. One may purposefully plan to assemble molecules that are capable of absorbing molecules from the gas phase and, possibly, to react with them. Reaction implies *sensing* and could be exploited to detect molecules, if there is a measurable response from the solid state. If the reaction is quantitative and reversible, the same processes can be used to trap gases and deliver them where appropriate. The control on solid-state reactions, that can be used to trap environmentally dangerous or poisonous molecules, is an attractive goal for solid-state chemistry and crystal engineering.

5. Conclusions

In 2003 CE is a booming field of research, which has definitely expanded from its inorganic and organic solid–state chemistry origins, to encompass many of the neighboring areas of solid-state and materials science. Crystal engineering is solid-state chemistry, or, better then that, it is an evolutionary step of solid-state chemistry. The advancement results as a sort of cultural *hybridization* between supramolecular chemistry, eg, the chemistry of intermolecular bonding, and the chemistry of molecular materials, eg, the utilitarian, application oriented side of molecular aggregation. Hence, CE belongs to chemistry, as only the chemists know how to synthesize, isolate, and characterize molecules and to assemble molecules in a bottom-up approach to larger and more complex aggregates. CE shares with supramolecular chemistry the idea that the collective properties of the solid aggregates depend on the choice of intermolecular and interion interactions between components, and are attained via processes of self-recognition and assembly (although crystallization is often under kinetic control). CE shares with materials chemistry the goal of preparing functionalized crystalline materials. Crystal-oriented synthetic strategies are finding applications in various directions, from nanoporous and meso-porous systems to ionic networks and molecular materials for applications in magnetism, but also in nonlinear optics, conductivity, solid-state sensors, etc. One can expect that these target properties will all be at the forefront of research in materials chemistry in the coming years. In this respect, it is apparent that organometallic and coordination compounds represent an extraordinary source of new building blocks for crystal construction and, therefore, of new or improved solid-state properties.

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